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EXAMINER

ART UNIT	PAPER NUMBER
1813	4

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire Three month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-19 are pending in the application.
   Of the above, claims 17-19 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-19 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-16, drawn to inactivated respiratory syncytial virus (RSV), method of preparing RSV, and method of immunizing, classified in Class 424, subclass 211.1.

II. Claims 17-19, drawn to diagnostic assays and kit, classified in Class 435, subclass 7.1.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the diagnostic assays of group II can be practiced with another materially different product such as purified viral proteins.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Michael Stewart on August 31, 1995 a provisional election was made with traverse to prosecute the invention of group I, claims 1-16. Affirmation of this election must be made by applicant in responding to this Office action. Claims 17-19 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

The PTO-1449 submitted with this Application had a note attached that copies of the references were to follow. These references have not been received. However, the references which were of record in the parent Application SN. 08/102,742 have been considered and the PTO-1449 has been initialed. Reference numbers 30-34 on the PTO-1449 were not of record in the parent Application and, since they have not been received, these references have been lined through.

Claims 1-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-16 of copending application Serial No. 08/472,174. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

Claims 5, 7, and 8 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The properties of the immunogenic composition prepared by the claimed method are not clear. The claims are drawn to a method which involves inactivating a purified virus to obtain a composition containing a "non-infectious and immunogenic RS virus" (claim 5). One of skill in the art would interpret the composition of these claims as being a whole virus. However, it is not clear that the treatment of a purified respiratory syncytial (RS) virus with a non-ionic detergent would result in a composition containing a whole virus or whether it would result in a composition containing solubilized viral proteins which resembles a subunit vaccine. Ewasyshyn et al teach that the viral envelope glycoproteins are solubilized by octylglucoside (i.e. n-octyl-β-D-glucopyranoside) (p 3). Ewasyshyn et al specifically disclose treating the pelleted virus for 1.5 hours with 2% v/v Triton X-100 and that alternately octylglucoside may be used (p 6). The specification teaches treating purified RSV with n-octyl-β-D-glucopyranoside (p 10). Specifically, the specification discloses treating the virus with 1% w/v n-octyl-β-D glucopyranoside for two hours. Therefore, it is not clear that the claimed method results in an inactivated whole RSV or whether it results in a composition consisting of solubilized RSV proteins. Because the non-ionic detergent would be expected to solubilize the viral proteins, the composition resulting from treating the purified virus with a non-ionic detergent would be a different composition than RSV treated with β-propiolactone or ascorbic acid and therefore the meaning of the terms "non-infectious and immunogenic RS virus" (claim 1) or "purified inactivated RS" when using non-ionic detergents as inactivating agents is not clear.

In claim 12, the step of "pelleting the ultrafiltered material" is not clear because the specification teaches that the RSV in the retentate is pelleted (p 15, Examples V and IV). The

phrase "pelleting the ultrafiltered material" implies that the filtrate (i.e. flowthrough material) is centrifuged.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The specification teaches the preparation of an inactivated respiratory syncytial virus (RSV) vaccine (p 7-11 and 13-17). The specification discloses that the administration to cotton rats of vaccines inactivated by n-octyl-β-D-glucopyranoside (OG), β-propiolactone (BPL), or ascorbic acid results in the formation of neutralizing serum antibody titers and protection upon challenge as measured by pulmonary virus titer (p 17-22). The specification discloses that the OG-inactivated vaccine does not result in enhanced pulmonary pathology (p 18-19). The specification states "Enhanced pulmonary pathology for β-propiolactone-inactivated RSV preparation was determined as in Example IX above" (p 20, line 21). However, the results of these experiments are not presented. The specification does not teach that the ascorbic acid-inactivated vaccine does not result in enhanced pulmonary pathology.

The cotton rat model used by Applicants has been used with some success as a model for disease potentiation by formalin-inactivated RSV as taught by Chanock et al (p 140, column 1,

second paragraph). Because Applicants' invention is also an inactivated RSV vaccine, the effect of these vaccines on pulmonary pathology could effectively be tested using the cotton rat model. However, the effectiveness of the vaccine based on results achieved in the cotton rat model may not necessarily be extrapolated to humans for the reasons which follow. McIntosh et al teach that although every subhuman primate species that has been examined can be infected by intranasal instillation of RSV, only the chimpanzee and owl monkey develop symptoms of infection. McIntosh et al also disclose that a satisfactory animal model of the lower respiratory tract illness seen most commonly in human infants has not yet been found (p 1051, column 2, paragraph 3). Collins et al disclose that the response to RSV infection in the chimpanzee most closely resembles that of humans with regard to the quantity and duration of virus shedding and the development of clinical disease (paragraph bridging pages 164 to 165). Collins et al teach that while nearly complete resistance to challenge with RSV infection was induced by immunization with vaccinia-RSV recombinants in cotton rats and owl monkeys, the vaccine had poor efficiency in chimpanzees (p 166, column 2). Collins et al also state that because of the permissiveness of the chimpanzees for RSV replication it seems likely that restriction of RSV replication would be more difficult to achieve in chimpanzees, and in infants and children, than in monkeys and rodents. Collins et al continue by stating that information obtained solely from monkeys and rodents might provide an overly optimistic assessment of candidate RSV vaccines (p 167, column 2, paragraph 2). In a recent review article on RSV vaccines, Hall states the following:

> "Currently there is no accurate way to predict the response of infants to a candidate vaccine before actual administration. Are there measurable parameters that correlate with an immune response that is protective, durable or detrimental? We do not even know

> what type of immune response would be safe and protective in young infants. Evidence has accumulated that certain serum antibodies are beneficial and protective, but they are only one part of the collage of RSV immunity, as indicated by the virus's ability to infect some infants with high titers of maternal antibody." (p 1394, column 2).

Therefore, in view of the above teachings, protection observed in the cotton rat model cannot be extrapolated to humans. Due to the unpredictability of RSV vaccines to provide protection in humans, it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans.

Claims 1-4 and 15-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above in the objection to the specification.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. As stated above, the specification does not teach that the BPL-inactivated vaccine does not result in enhanced pulmonary pathology because the results of the experiments are not presented. The specification also does not teach that RSV inactivated with either ascorbic acid or an non-ionic detergent other than octylglucopyranoside does not result in enhanced pulmonary pathology. In view of the potentiation of disease by the formalin-inactivated vaccine, it is not predictable whether the BPL-inactivated vaccine would have a similar effect thus making this form of inactivation unsuitable for use as a vaccine in humans. Chanock et al propose that the disease potentiation by the inactivated RSV vaccine appears to have occurred because formalin

inactivation selectively reduces the antigenicity of protective epitopes present on the RSV F surface glycoprotein (p 139 column 2, paragraph 1). In an article on the action of BPL, Budowsky et al (Vaccine 9: 319-325) teach that the action of any chemical agent on viruses modifies not only the nucleic acid responsible for infectivity but also viral proteins and glycoproteins (p 321, column 2). Therefore, it would not be unexpected that BPL or ascorbic acid could similarly modify the RSV F surface glycoprotein and result in the potentiation of disease such as was observed with formalin. Neugebauer teach that although trends in the behavior of simple detergent/solvent system can be predicted from theory, no global explanation of the interaction of detergents with biomacromolecules exists. Neugebauer states that the task of finding the best detergent for a particular application is usually accomplished by trial and error (p 253, paragraph 2). Therefore, it is not predictable other non-ionic detergents would have the same effect on the RSV glycoproteins as octylglucopyranoside and whether the results of inactivation with other non-ionic detergents would be the same as octylglucopyranoside in terms of pulmonary pathogenicity. In the absence of evidence to the contrary, the ability of a BPL-inactivated, ascorbic acid-inactivated, or other non-ionic detergent-inactivated vaccines to provide protection from RSV infection in humans without causing increased pathogenicity is unpredictable.

Claims 1-7, 9, and 10-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 1 is rejected under 35 U.S.C. § 102(e) as being anticipated by Bordt et al.

Bordt et al teach a bovine respiratory syncytial virus which is inactivated with ascorbic acid column 2, lines 10-19 and column 6, lines 52-56). While Bordt et al is silent as to whether the virus is substantially free from cellular and serum components, the product of Bordt et al appears to be in a purified state, and hence the same as the claimed composition, because it is to be administered as a vaccine.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 2-4, 15 and 16 are rejected under 35 U.S.C. § 103 as being unpatentable over Bordt et al in view of McIntosh et al.

Bordt et al teach a vaccines against viruses, including paramyxoviruses, which are inactivated with ascorbic acid (column 2, lines 10-19). Bordt et al teach the administration of the vaccine to humans for preventing disease (column 1, lines 64-67). Bordt et al teach that the vaccine may include adjuvants (column 2, lines 41-45). Bordt et al do not specifically teach the route of administration or the population to which the vaccine is to be administered. Bordt et al also do not specifically disclose human respiratory syncytial virus.

McIntosh et al teach that human respiratory syncytial virus is the most important cause of viral lower respiratory tract disease in infants and children and that human RSV is a paramyxovirus (p 1045).

It would have been obvious to one of ordinary skill in the art to inactivate human RSV for use as vaccine because Bordt et al teach that paramyxoviruses may be inactivated with ascorbic acid and RSV is a paramyxovirus as taught by McIntosh. It would have been obvious to administer the vaccine to the people in need of such a vaccine such as infants and children as

taught by Mcintosh. Finally, oral, intranasal, or injectable forms and routes of administration would be obvious because vaccines are routinely administered in these ways.

Claims 5 and 6 are rejected under 35 U.S.C. § 103 as being unpatentable over Downing et al in view of Preston et al.

Downing et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing RSV on a cell line; 2) harvesting the grown virus; 3) purifying the virus under non-denaturing conditions to produce a virus substantially free from cellular and serum components (p 217-218 and 211). The purification procedure involved ion exchange chromatography followed by sucrose gradient centrifugation (p 211, paragraph 2). Downing et al do not teach inactivating the virus with β-propiolactone.

Preston et al teach the inactivation of RSV by treatment with β-propiolactone (paragraph bridging p 819-820).

It would have been obvious to one of ordinary skill in the art to inactivate the RSV purified by the method of Downing et al with β-propiolactone because β-propiolactone is effective in inactivating RSV as taught by Preston et al. Furthermore, one of skill in the art would inactivate a virus for an immunogenic composition to prevent the host from becoming infected with the virus.

Claims 5 and 9 are rejected under 35 U.S.C. § 103 as being unpatentable over Downing et al in view of White et al.

The teachings of Downing et al are set forth above. Downing et al do not teach inactivating the virus with ascorbic acid.

White et al teach the inactivation of RSV by treatment with ascorbic acid (paragraph bridging pages 529-530). White et al teach that the use of ascorbic acid as an inactivating agent has the advantages of being less expensive and more readily available than gamma radiation and is not carcinogenic as is β-propiolactone (p 530, paragraph bridging columns 1 and 2).

It would have been obvious to one of ordinary skill in the art to inactivate the RSV purified by the method of Downing et al with ascorbic acid because ascorbic acid is effective in inactivating RSV and has the advantages taught by White et al and set forth above. Furthermore, one of skill in the art would inactivate a virus for an immunogenic composition to prevent the host from becoming infected with the virus.

Claims 5, 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Downing et al in view of Prince and Georgiades et al.

The teachings of Downing et al are set forth above. Downing et al do not teach inactivating the virus with a non-ionic detergent, specifically n-octyl-β-D-glucopyranoside.

Prince teaches the inactivation of plasma hepatitis virus by treatment with a non-ionic detergent and cite n-octyl-β-D-glucopyranoside as one of the detergents which may be used in the method (column 4, lines 37-39 and column 5, line 33). Prince teaches that the advantages of using non-ionic detergents is that they are non-denaturing and are not carcinogenic (sentence

bridging columns 2 and 3). Georgiades et al teach the inactivation of contaminating viruses in interferon alpha solutions by treatment with non-ionic detergents (column 4, lines 1-16).

It would have been obvious to one of ordinary skill in the art to inactivate the RSV purified by the method of Downing et al with by treatment with n-octyl-β-D-glucopyranoside because non-ionic detergents are capable of inactivating viruses as taught by Prince and Georgiades et al and have the advantage of being non-denaturing to proteins and non-carcinogenic as taught by Prince. Furthermore, one of skill in the art would inactivate a virus for an immunogenic composition to prevent the host from becoming infected with the virus.

Claims 5, 10, 12 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al.

Ewasyshyn et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing the virus in a medium virtually free of exogenous serum proteins on a tissue culture cell substrate that is readily acceptable for use in human vaccine production (paragraph bridging p 3 and 4); 2) harvesting the virus; and 3) purifying the virus by, a) filtration to remove cell debris, b) concentration by tangential flow ultrafiltration using a 100 kD nominal molecular weight cut off membrane, and c) pelleting the ultrafiltered material by ultracentrifugation (p 3, lines 10-13 and p 5, line 34 to p 6, line 9). Ewasyshyn et al do not teach further purifying the virus using sucrose density gradient centrifugation. Ewasyshyn et al do not teach inactivating the virus for formulation as an immunogenic composition.

Mbiguino et al teach purifying RSV under non-denaturing conditions using a sucrose gradient (p 163 third paragraph and p 165 first paragraph).

It would have been to purify RSV using the method taught by Ewasyshyn et al with a further step of sucrose density gradient centrifugation as taught by Mbiguino et al because sucrose gradient centrifugation is an effective means of preparing pure RSV and a highly purified virus would be optimal for an immunogenic composition to prevent the formation of antibodies against contaminating proteins. It would also have been obvious to inactivate the RSV for an immunogenic composition to prevent the host from becoming infected with the virus.

Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al as applied to claims 5, 10, 12 and 13 above, and further in view of McIntosh et al and Paradiso et al.

The teachings of Ewasyshyn et al and Mbiguino et al are set forth above. It would have been obvious to purify RSV using the method taught by Ewasyshyn et al with a further step of sucrose density gradient centrifugation as taught by Mbiguino et al for the reasons discussed above. It would also have been obvious to inactivate the RSV as discussed above. The above cited art do not specifically teach growing RSV on cells from the VERO cell line.

McIntosh et al teach that RSV may be successfully grown in VERO cells (p 1051, paragraph 2). Paradiso et al teach that highly immunogenic protein may be prepared from RSV grown in Vero cells (column 21, lines 1-30).

It would have been obvious to grow RSV in VERO cell lines as an alternative cell line for growing RSV because highly immunogenic proteins from RSV may be obtained from RSV grown in VERO cells as taught by Paradiso et al.

Claim 14 is rejected under 35 U.S.C. § 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler.

Ewasyshyn et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing the virus in a medium virtually free of exogenous serum proteins on a tissue culture cell substrate (paragraph bridging p 3 and 4); 2) harvesting the virus; and 3) purifying the virus by, a) filtration to remove cell debris, b) concentration by tangential flow ultrafiltration using a 100 kD nominal molecular weight cut off membrane, and c) pelleting the ultrafiltered material by ultracentrifugation (p 3, lines 10-13 and p 5, line 34 to p 6, line 9). Ewasyshyn et al do not teach further purifying the virus using gel filtration and ion-exchange chromatography. Ewasyshyn et al do not teach inactivating the virus for formulation as an immunogenic composition.

Downing et al teach a method of purifying RSV using ion-exchange chromatography (paragraph bridging pages 217-218) Downing et al teach that gel filtration chromatography may be a useful complimentary technique for further purification after initial density gradient or affinity purification steps (p 226, last paragraph). Downing also exemplifies a purification procedure which involves ion-exchange chromatography followed by sucrose gradient centrifugation to increase the purity (p 221)

Kuchler teaches that there are three basic steps to the purification of viruses (p 184-194). The first is clarification (p 185). The second is concentration which may be performed by several methods including ultrafiltration (p 185). The third step is purification. Kuchler teaches that purification of viruses may be accomplished by chromatograph and ion-exchange resins, by molecular sieving on gel filtration columns, by countercurrent distribution or by gradient centrifugation (p 186, paragraph 4).

It would have been obvious to one of ordinary skill in the art to employ gel filtration and ion exchange chromatography to the method taught by Ewasyshyn et al in order to obtain a more purified RSV preparation for use as an immunogenic composition to avoid the generation of antibodies to contaminating proteins. The steps taught by Ewasyshyn et al are basically clarification and concentration steps according to the purification scheme taught by Kuchler. Because Downing et al teaches that RSV may be purified using ion-exchange chromatography and that gel-filtration may additionally be employed in purification procedures, one of ordinary skill in the art would have been motivated to use these two procedures, which are well known methods in virus purification, to remove the serum components when purifying RSV. Downing et al teaches a gel filtration step following other chromatography methods. However, in the absence of evidence to the contrary, performance of the chromatography steps in either order would be expected to have similar results. As stated above, it would also have been obvious to inactivate the RSV for an immunogenic composition to prevent the host from becoming infected with the virus.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie K. Staples whose telephone number is (703) 305-7556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 305-7939. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

JKS
Julie K. Staples, Ph.D.
September 28, 1995

HAZEL F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800